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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 022904

Application Number: 08/765,108
Filing Date: March 27, 1997
Appellant(s): KRIEGER ET AL.

Patrea L. Pabst
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed February 9, 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 11-13, 19-22, and 44-50 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Bowie et al., 1990, Science 247:1306-1310

Calvo et al., J. Biol. Chem 268(25)18929-18935, 1993

Cao, G., et al. J. Biol. Chem. 272(52)33068-33076, 1997

Degrave, W. et al., Molec. Biol. Rep. 11(57-61)1986

Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction (1993), Birkauser, Boston, pages 492-495.

Yang et al. (PNAS 87(7097-7911)1990)

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

(a) ***Claim Rejections - 35 USC § 112, first paragraph:***

(i) Claims 11-13, 19-22, 44-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, as set forth previously and reiterated below.

The specification discloses a hamster and a mouse polynucleotide of SEQ ID NO: 3 and 7, respectively, yet the claims encompass polynucleotides not described in the specification, i.e. polynucleotides sequences from other species, mutated sequences, allelic variants, or sequences that need only hybridize to SEQ ID NO: 3 or 7 under moderately stringent conditions yet which retain the required functional limitations. None of these sequences meet the written description provision of 35 U.S.C. 112, first paragraph. Although one of skill in the art would reasonably predict that these sequences exist or could exist, one would not be able make useful predictions as to the nucleotide positions or identities of those sequences based on the information disclosed in the specification.

The instant disclosure of a single polynucleotide from hamster and a single polynucleotide from mouse, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, only two polynucleotide sequences, which is not sufficient to describe the essentially limitless genera encompassed by the claims.

With the exception of the hamster and mouse polynucleotides referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed "scavenger receptor protein type BI" that are not encoded by SEQ ID NO: 3 or 7, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only the hamster and mouse polynucleotides, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Appellant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115). Further, claim 49 requires a compound that selectively inhibits binding of lipoprotein to the scavenger receptor protein type BI. There is no description of such a compound, and nor could one be envisioned based merely on a desired activity of the compound.

(ii) Claims 11-13, 19-22, 44-50 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids encoding a polypeptide of either SEQ ID NO: 4 or 8, does not reasonably provide enablement for nucleic acids encoding a scavenger receptor type BI protein other than SEQ ID NO: 4 and 8. Nor does the specification provide an enabling basis for a compound that selectively inhibits binding of lipoprotein to the scavenger receptor protein type BI, as required by claim 49. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims encompass an essentially limitless number of polynucleotides encoding polypeptide variants of the polypeptide of SEQ ID NO: 4 or 8, i.e. substitutions, deletions or insertions in a protein corresponding to SEQ ID NO: 4 or 8; yet the specification has not provided sufficient guidance as to how to make and use the encoded polypeptides which are not 100% identical to the polypeptide of SEQ ID NO: 4 or 8, but which still retain a desired

property of the polypeptide of SEQ ID NO: 4 or 8. The specification discloses two naturally occurring polynucleotides encoding scavenger receptor protein type BI proteins, which selectively bind to low density lipoprotein and to modified lipoprotein, from two species of rodents, yet the vast majority of polypeptides required by the claims are amino acid sequence variants of SEQ ID NO: SEQ ID NO: 4 or 8 - artificially produced versions of SEQ ID NO: 4 and 8 and naturally occurring allelic variants of SEQ ID NO: 4 and 8, as well as homologs of SEQ ID NO: 4 and 8 from other species, including allelic variants of those undisclosed species homologs. The specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make without destroying the receptor's unique activities. Furthermore, the specification has not provided guidance as to what properties of the allelic variants or sequence variants of the protein corresponding to SEQ ID NO: 4 or 8 might be desired nor any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property. Appellant has not defined a difference in structure or difference in function between the protein corresponding to SEQ ID NO: 4 or 8 and variants of said protein. If a variant of the protein corresponding to SEQ ID NO: 4 or 8 is to have a structure and function similar to the protein corresponding to SEQ ID NO: 4 or 8, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein corresponding to SEQ ID NO: 4 or 8. Conversely, if a protein variant of SEQ ID NO: 4 or 8 need not have a disclosed property, then the specification has failed to teach how to use such a variant.

The analysis of the issues above, 10(a)(ii), will be divided into four parts. Part (a) will analyze enablement for artificially constructed mutants of the disclosed sequences, part (b) will

analyze enablement for species homologs of the disclosed sequences, part (c) will analyze enablement for allelic variants of the disclosed sequences, and part (d) will analyze enablement for the administration of a compound that selectively inhibits binding of lipoprotein to the scavenger receptor protein type BI, as required by claim 49

10(a)(ii)(a) The specification has failed to teach how to make and use artificially constructed variants of SEQ ID NO: 4 or 8 without undue experimentation. Claims 11-13, 19-22 and 44-50 place very little in the way of structural limitations on the required scavenger receptor type BI protein. The claims are, in essence, single means claims, because the claims encompass any composition having the recited activities whereas the instant specification only discloses those two naturally occurring compositions known to the inventor, i.e. SEQ ID NO: 3 and 7. In *In re Hyatt*, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983), a single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claim because the specification at most disclosed only those means known to the inventors. When claims depend on a recited property, a fact situation comparable to *Hyatt* is possible, where the claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor. See also *Fiers v. Sugano*, 984 F.2d 164, 25 USPQ2d 1601 (Fed. Cir. 1993), and MPEP § 2164.08(a). With regard to enablement for artificially constructed variants of the polypeptides encoded by SEQ ID NO: 3 or 7, the instant fact pattern is actually one step deficient and removed from that of *Hyatt*. The instant specification does not disclose any working examples of artificially constructed variants of the polypeptides encoded by SEQ ID NO: 3 or 7.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2). However, the specification has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Further, although the specification mentions that various computer programs could be used in the search for important structural portions of the proteins, it is well recognized in the art that such programs are not sufficient to reliably predict the structural, let alone functional, aspects of a protein based on amino acid sequence, see Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction (1993), Birkauser, Boston, pages 492-495.

Although the skilled artisan is aware of many art-recognized procedures for producing variants, as suggested at page 39, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a

starting point for further experimentation. Even if an active or binding site were identified in the specification, which there appears not to be, these may not be sufficient, as the skilled artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The specification has merely offered the skilled artisan an invitation to embark on a plan of essentially random trial and error experimentation, wherein in variants are produced by randomly selecting amino acids for substitution, deletion or insertion, and then testing these variants to try to find those that meet the limitations of the claims. Such experimentation is undue and would not be seen by one of skill in the art to be routine.

Thus, due to the large quantity of experimentation necessary to generate the infinite number of variants required by the claims and then to screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any meaningful structural limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope

10(a)(ii)(b) The specification has not provided an enabling disclosure for species homologs of SEQ ID NO: 3 and 7. The claims encompass, and claim 19 specifically requires, polynucleotides encoding scavenger receptor protein type BI proteins from other species. The specification discloses two cDNA sequences from closely related rodent species, however, the

specification provides no more than an invitation to the skilled artisan to begin a research plan to try to identify polynucleotides from other species, particularly that of human (e.g. pg 38-40). The specification merely hints at, and in only a generalized way, that the skilled artisan could the use the disclosed polynucleotide sequences to screen cDNA libraries or genomic DNA libraries to obtain the required polynucleotides. The skilled artisan would immediately appreciate that such generalized instructions do not enable one skilled in the art to obtain the required polynucleotides. Specific information, not generalized suggestions, are required by the skilled artisan to obtain the claimed polynucleotides without considerable trial and error experimentation. Using the specification as a guide, the skilled artisan would additionally need to answer a multitude of questions that cannot be arrived at in a straight forward manner. It is very easy to make the statement that the cDNA and/or genomic libraries can be used to obtained the polynucleotide (e.g. pg 38), it is a wholly different matter, however to discover which cDNA library to use or which genomic DNA library to use- or which tissues to use to make such a cDNA library, or how to make and screen a genomic DNA library that could be expected to yield a gene encoding a protein as large as that of the disclosed scavenger receptor protein type BI proteins. The difficulty in answering such questions is further compounded by the fact that the artisan is provided no specific teaching as to parts of the disclosed polynucleotides that should be used as probes and under what conditions should the probes hybridize in order to isolate the required polynucleotides away from the many related polynucleotides that would be expected to hybridize under moderately stringent conditions in libraries constructed from non-rodent species. At page 38, the specification merely indicates that specific "regions of interest" are those of the nucleotide sequence which encode regions of the protein conserved between different receptors;

between the same receptors for different species; and with discrete regions of the receptor proteins, e.g. cytoplasmic region, transmembrane region, etc.. The skilled artisan would view these teachings as simply generalized advice and not the specific information required to make probes that can be used to find homologs from other species. Thus, the artisan might have the right library, and not know it because he has the wrong probes; conversely, the probes may be correct, if only he could find the correct tissues with which to make the library. The specification offers essentially no specific help in this regard. To the contrary, the specification attests to the complex and unpredictable state of this art. For example, the hamster cDNA was obtained from a library that was generated from a rare variant of CHO cells, var-261, based on the apparently novel polyanion binding properties of the cells, yet it turned out that the cDNA that was isolated, and is now the subject of interest, was not responsible for this activity - which apparently still remains a mystery, see page 27. Further, the tissue specific expression of this mRNA appears to be complex and not well understood. While Northern analysis appeared to indicate that the mRNA was expressed in adipose tissues, western analysis suggested that it was not - and that a different polynucleotide must have cross-hybridized strongly with the probe in adipose tissues (see page 32, beginning at L25). Thus, the expression of this polynucleotide appears to be confusing enough in those tissues examined and disclosed in the instant specification - what might be found in a human, for example, is simply beyond reasonable extrapolation.

10(a)(ii)(c) The specification does not provide and enabling basis for allelic variants of SEQ ID NO: 3 or 7. The clams encompass naturally occurring allelic variants of SEQ ID NO: 3 or 7, yet the specification failed to teach where to look for naturally occurring allelic variants of

SEQ ID NO: 3 or 7, e.g. no specific disorder or specific phenotype has been asserted to correlate with a naturally occurring allelic variant, such that the artisan might know where to obtain a variant. The specification merely offers the skilled artisan the invitation to randomly try to find variants through trial and error sampling of animal populations. Such random trial and error experimentation is unduly burdensome.

10(a)(ii)(d) The specification does not provide an enabling basis for the administration of a compound that selectively inhibits binding of lipoprotein to the scavenger receptor protein type BI, as required by claim 49. The specification provides no such compound, but merely an invitation to find such a compound, if such a compound can be found. One highly skilled in the art appreciates that the screening assays described on pages 43-54 are useful for determining whether or not a compound selectively inhibits binding of lipoprotein to the scavenger receptor protein type BI; and although they are useful in the search for such compounds, they do not automatically produce the compounds. The invitation to use these assays to search for compounds having the desired properties is simply an invitation for further research and investigation to randomly sample any and all compounds for the desired activity. Such random experimentation is unduly burdensome.

(b) ***Claim Rejections - 35 USC § 112, second paragraph:***

Claims 11-13, 19-22, 44-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Appellant regards as the invention, as set forth previously for the following reasons:

(b1) Claims 11 and 50 and dependent claims 12, 13, 19-22 require, a "functional" scavenger receptor protein type BI (claim 11), or method comprising determining "the function" of scavenger receptor protein type BI (claim 50). As used in the art to describe a newly isolated protein that has been characterized in various in vitro assays, the word "function" is of dubious value in establishing and describing the sphere of biologic properties that a protein may have in an intact organism. The word "function" implies more than a list of physical properties, and is more akin to the idea of a biologic role for the protein. The instant specification has not set forth what aspects of the scavenger receptor protein type BI define its function or biologic role. The specification, at pages 29-30, merely hints at, and in a generalized way, potential biologic roles for the protein, e.g. that the data provide support "for the potential role of this receptor in lipoprotein and lipid metabolism", see page 29, Lines 19-20. In fact, the specification as filed (other than claim 50) does not appear to use the word "function" in relation to the scavenger receptor protein type BI. Thus, the artisan could not reasonably and unambiguously know whether or not he or she was practicing the claimed invention, because he or she would not know what is meant by the term "function" or "functional" in relation to the claims.

(b2) Claims 11-13, 19-22, 44-50 require a vast, and essentially limitless, number of proteins that are "scavenger receptor protein type BI" proteins, yet the claims do not set forth that element or combination of elements that is unique to or definitive of a "scavenger receptor protein type BI". As currently worded, the melting temperature of the perfectly base-paired double stranded DNA provides the reference temperature with which the nucleic acid encoding the "scavenger receptor protein type BI" must hybridize, i.e. at 25°C below the melting temperature of the perfectly base-paired double stranded DNA. Thus, the melting temperature of

the perfectly base-paired double stranded DNA determines the bounds of the claims. If, for example, the perfectly base-paired double stranded DNA were very long and have a high GC content, then it would have a higher melting temperature than a perfectly base-paired double stranded DNA that was shorter or had less GC content. The higher the melting temperature of the reference perfectly base-paired double stranded DNA, the higher the hybridization temperature and thus the number of potential molecules that could hybridize to SEQ ID NO: 3 or 7 would diminish as the melting temperature increased. These facts are clearly articulated by the specification at pg 40, Lines 18-35. The problem with the claims is that they do not set forth *which* perfectly base-paired double stranded DNA *is* the reference polynucleotide. And nor do the claims or specification indicate that *any* perfectly base-paired double stranded DNA could serve as the reference DNA, as one skilled in the art would not expect that to be possible and would not consider that to be a reasonable interpretation of the claims. Therefore, in the vast continuum of hybridization conditions required by the claims, it is unclear what conditions are meant to provide meaning and definitiveness to the phrase "scavenger receptor protein type BI". One of ordinary skill in the art would view the teachings of the specification at pg 40, Lines 18-35, as they relate to hybridization to SEQ ID NO: 3 or 7, to mean that the reference polynucleotide ***is*** a perfectly base-paired double stranded DNA consisting of SEQ ID NO: 3 or 7. Yet, this is not what is currently being claimed. See suggested claim language below.

Furthermore, claim 11 requires "moderately stringent conditions" whereas claim 13 requires "stringent" conditions, yet each recite that the conditions are that produced at a temperature of approximately 25°C below the melting temperature of the perfectly base-paired

double stranded DNA. Thus, it is unclear what difference is meant, if any, between the "moderately stringent conditions" of claim 11 and the merely "stringent" conditions of claim 13.

Additionally, claims 11, 44, 48 and 49 recite the limitation "which selectively binds to low density lipoprotein and to modified lipoprotein". This phrase is not sufficient, either alone, or in conjunction with the other limitations recited in the claims, to provide a meaningful definition of the phrase "scavenger receptor protein type BI". Further, the specification does not teach that these limitations are definitive of a "scavenger receptor protein type BI". At page 10, line 39 bridging page 11, the specification teaches that hsSR-BI differs from CD36 and other modified lipoprotein receptors described to date in that its binding of AcLDL is inhibited by native LDL.

It is suggested to Appellant that the following claim language would meet the requirements of 35 U.S.C. 112, second paragraph, as well as distinguish the claimed polynucleotides from those encoding CD36. Rejections under 35 U.S.C. 112, first paragraph, would, however, still apply.

Claim 11. An isolated nucleic acid molecule encoding a scavenger receptor protein type BI which selectively binds to low density lipoprotein and to modified lipoprotein having the characteristics of acetylated low density lipoprotein in cell media containing 10% serum, wherein the binding of AcLDL to said scavenger receptor protein type BI is inhibited by native LDL, and which isolated nucleic acid molecule hybridizes to SEQ ID NO: 3 and 7 under moderately stringent hybridization conditions at a temperature of approximately 25°C below the

melting temperature of a perfectly based-paired double stranded DNA molecule consisting of SEQ ID NO: 3 or 7.

(c) Claim Rejections - 35 USC § 102

Claims 11, 13, 19, 20 and 22 rejected under 35 U.S.C. 102(a) as being anticipated by Calvo et al., J. Biol. Chem. 268(25)18929-18935, Sept. 05, 1993.

Figures 2 and 3 on pages 18931 and 18932 of Calvo provide the nucleotide sequences of a recombinant nucleic that Appellant has admitted is the human equivalent of the mouse and hamster SR-BI, e.g. the Declaration filed 1/5/98 (Paper 9), that would be expected to hybridize under the conditions of the claims, absent evidence to the contrary. Further the labeled nucleic acid of claim 20 can be found in Figure 5 on page 18993. Additionally, host cells comprising the isolated nucleic acid (claim 22) were used in the cloning and sequencing of the nucleic acid, e.g. col 1 of page 18932.

(d) Claim Rejections - 35 USC § 103

Claims 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Calvo et al., J. Biol. Chem. 268(25)18929-18935.

(i) Claim 21 requires an expression vector comprising the polynucleotide of claim 11. As discussed above, Calvo et al. teach the polynucleotide of claim 11 in Figures 2 and 3 encoding the CLA-1 protein.

(ii) Calvo et al. do not express the full length polynucleotide of claim 11, instead Calvo et al. expressed the polynucleotide encoding the carboxyl terminal of CLA-1 as a fusion with CD36 because antibodies to the CLA-1 protein were not available (pg 18933, col 1). Calvo believed that it was the C-terminal of CLA-1 that would be responsible for the sub-cellular localization; thus, they used antibodies to CD36 that were available to them to determine the localization of the CLA-1/CD36 hybrid. They found that the hybrid was expressed predominantly in the plasma membrane and concluded that native CLA-1 would also be expressed in the membrane (see page 18933, col. 2), such an expressed native CLA-1 would meet the limitations of claim 21.

(iii) Therefore, it would be obvious to one of ordinary skill in the art, i.e. a biomedical research scientist, to express the CLA-1 protein by incorporating the cDNA described therein into an expression vector and heterologous host by employing those methods which are routine in the art at the time the invention was made to permit the quantitative production of CLA-1 and to facilitate its characterization at the molecular level with a reasonable expectation of success. The motivation to do so was to conduct assays for binding partners of the polypeptide as suggested in col 2 page 1893 of Calvo, as would be commonly understood in the art.

(11) Response to Argument

(a)(i)(a) Response to Appellant's arguments regarding the claimed invention, as set forth in item 8(a) of the Brief (page 7): Appellant argues that the SR-BI protein is defined in the specification by its three dimensional structure, as in Figure 1B. This argument has been fully considered but not deemed persuasive. Appellant is reminded that Figure 1B is a simple two

dimensional line cartoon; proteins are not simple cartoons. The only descriptions of a functional structure disclosed by the specification are the primary structures of the hamster and mouse SR-BI proteins as set forth in SEQ ID NO: 4 and 8; no three-dimensional structure has been described for these proteins. No particular structural feature has been asserted to correlate with any functional binding activity. Further, Appellant's discussion of the tissue specific expression of the SR-BI proteins appears to be confined to the two rodent species, there is no mention of human tissue distribution and no mention as to where to find a human cDNA.

(i)(b) Claims 11-13, 19-22, 44-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, as set forth above in item 10(i).

At page 36 of the Brief, Appellant argues the written description requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular known structure. This argument has been fully considered but not deemed persuasive, the issue here is that the specification has not put forth a particular structure(s), present in each member of the vast and disparate genus claimed, that is asserted to correlate with a function. The mere recitation that the polynucleotide hybridize under moderately stringent conditions does not stipulate or describe any particular structure or function - it simply provides some constraint on the possible deviation in structure that is allowed, although this constraint is fairly small when one considers that the hybridization conditions allow for an essentially limitless number of variants. Thus, regarding a structure/function correlation, there is no particular structure/function correlation between any variant of SEQ ID NO: 3 or 7 and any particular function.

Appellant argues that it is now well established at this point that once one provides the structure and function, and has reduced to practice representative species of a genus, one has complied with the written description requirement. This argument has been fully considered but not deemed persuasive because the instant specification has not correlated any structure other than that encoded by SEQ ID NO: 3 and 7 with a function, yet the claims encompass a vast genus of structures that have no correlation with a function. Particularly, there is no disclosure of a human SR-BI structure to correlate with the required function. Appellant is referred to a recent decision by the U.S. Court of Appeals for the Federal Circuit, *Noelle v. Lederman et al.*, Interference No. 104,415, decided January 20, 2004, wherein the fact pattern closely resembles the instant fact pattern. While the claims in that case were directed to antibodies, the decision was based on whether or not Appellant (*Noelle*) was in possession of the protein that the antibodies would be raised against. *Noelle* had described the murine protein and an antibody, but the claims were to a human antibody that bound to the human homolog of the murine protein. The court stated that if *Noelle* was in possession of the human protein, then antibodies to the human protein would be adequately described. However, the court determined that simply disclosing the murine protein did not put *Noelle* in possession of the human protein. There is no reason to think that the court would have found that *Noelle* was in possession of the human protein if *Noelle* had also described a hamster protein, as in the instant case. To the contrary, the court agreed with the definition of the written description requirement as set forth in *Vas-Cath*, 935 F.2d at 1563-64, and quoting *Fiers v. Revel* 984 F.2d 1164, 1170 (Fed. Cir. 1993), that statements in the specification describing the functional characteristics of a DNA molecule or methods of its isolation do not adequately describe a particular claimed DNA sequence. Instead

"an adequate written description of DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself."

Appellant's arguments at page 37 regarding an alleged reduction to practice of the human SR-BI have been substantially addressed above and are not persuasive. Appellant's additional arguments on page 37 of the Brief regarding claim 19 do not appear to be germane to the basis of the rejection as set forth in item 10(i) above.

In the paragraph bridging page 38 and 39 of the Brief, Appellant misconstrues the facts in *Regents of U.C. v. Lilly*. Example 6 of the 4,652,525 patent (*Regents of U.C.*) describes the isolation of the human cDNA using the methods disclosed in Examples 1-4 which were used successfully to clone the rat cDNA. The court found that specification did not provide a written description of the human cDNA. The instant specification is actually deficient in two significant ways when compared to the disclosure in the 4,652,525 patent. The 4,652,525 patent teaches which human tissues to use to find the cDNA. As set forth above, there is no such teaching in the instant specification. Calvo et al. (supra) found the cDNA in a human placental library. There no teaching in the instant specification to look for a cDNA in a human placental library. The 4,652,525 patent teaches the amino acid sequence of the human protein. There is no teaching of any human SR-BI molecules in the instant specification. One of ordinary skill in the art appreciates that knowledge of the human protein sequence would be an advantage in the cloning of the human cDNA, yet Appellant attempts to frame this knowledge as some how being a disadvantage – ignoring the fact that the 4,652,525 discloses the corresponding rodent cDNA – just as in the instant specification. Likewise, it is expected that the court will view Appellant's

claim to the human DNA as lacking an adequate written description, as it had done regarding the 4,652,525 patent, which actually provides more information as to the human homologue than does the instant specification.

Appellant's arguments on pages 39-42 of the Brief regarding claims 44-50 have been fully considered but are not persuasive. The claims require the use of a genus of SR-BI proteins that Appellant was not in possession of at the time of filing, as set forth above.

.

(a)(ii) Claims 11-13, 19-22, 44-50 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids encoding a polypeptide of either SEQ ID NO: 4 or 8, does not reasonably provide enablement for nucleic acids encoding a scavenger receptor type BI protein other than SEQ ID NO: 4 and 8. Nor does the specification provide an enabling basis for a compound that selectively inhibits binding of lipoprotein to the scavenger receptor protein type BI, as required by claim 49. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. As above in item 10(a)(ii), the response to Appellants arguments will be divided among four subject areas, a-d.

(a) The specification has failed to teach how to make and use artificially constructed variants of SEQ ID NO: 4 or 8 without undue experimentation, as set forth above in item 10(a)(ii)(a).

Regarding this aspect of the rejection, at page 11 of the Brief, Appellant requests that the examiner consider the Board of Appeals decision in the parent case (U.S.S.N. 08/265,429) and

argues that no more disclosure is contained in the present application than in the parent case. This argument has been fully considered but not deemed persuasive. Appellant is reminded that there was no Board of Appeals decision in the parent case. Further, it is the instant claims that are under examination and not the claims in the parent case. Appellant argues that the examiner has failed to provide a reasonable explanation as to why the specification does not enable the claimed invention. This argument has been fully considered but not deemed persuasive. The examiner provided several reasons, restated above in item 10(a)(ii), yet Appellant has not indicated why these reasons are unreasonable

Appellant also addresses this issue beginning on page 20 of the Brief. Appellant argues that claims may encompass embodiments not explicitly described nor exemplified; and that some inoperative embodiments would not render the claims non-enabled. This argument has been fully considered but not deemed persuasive. The instant claims encompass an essentially limitless number of embodiments which have not been described, exemplified, or supported by enabling teachings. Further, the issue is not the potential number of inoperable embodiments; the issue is that the specification has failed to teach how to make a representative number of operable embodiments.

Appellant has taken the position that 35 U.S.C. 112, first paragraph, permits an artisan to present claims of essentially limitless breadth so long as the specification provides one with the ability to test any particular embodiment which is encompassed by the material limitations of a claim and thereby distinguish between those embodiments which meet the functional limitations from those embodiments which don't. This argument is not entirely without merit. However, the issue here is the breadth of the claims in light of the predictability

of the art as determined by the number of working examples, the skill level of the artisan and the guidance presented in the instant specification and the prior art of record. Appellant's "make and test" position is inconsistent with the decisions in *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) and *Amgen v. Chugai Pharmaceuticals Co. Ltd.* , 13 USPQZd, 1737 (1990) and *In re Wands*, 8 USPQZd, 1400 (CAFC 1988). *In re Wands* stated that the factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. All of these factors were addressed in the initial rejection. The text beginning on line 38 on page 38 of the instant application indicates that the "RSR-BI" refers to the nucleotide and amino acid sequences, respectively, shown in shown in Sequence ID Nos. 3 and 4, and 7 and 8, and degenerate variants thereof and their equivalents in other species of origin, especially human, as well as functionally equivalent variants, having additions, deletions and substitutions of either nucleotides or amino acids which do not significantly alter the functional activity of the protein as a receptor characterized by the binding activity identified above". Because any nucleic acid will "hybridize" to any other nucleic acid under some conditions, the current claims encompass isolated nucleic acids encoding non-naturally occurring proteins having an amino acid sequence which completely deviates from the two naturally occurring amino acid sequences disclosed in the instant specification. These claims encompass an unlimited number material embodiments. Breadth alone is not the issue, however. As set forth previously, *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970), held that

"Inventor should be allowed to dominate future patentable inventions of others where those inventions were based in some way on his teachings, since such improvement while unobvious from his teachings, are still within his contribution, since improvement was made possible by his work; however, he must not be permitted to achieve this dominance by claims which are insufficiently supported and, hence, not in compliance with first paragraph of 35 U.S.C. 112; that paragraph requires that scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific law; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved."

Having established the breadth of the claims, Wands now requires that one consider the number of working examples presented in the instant specification. Importantly, it is noted that there is not a single example in the instant specification, working or prophetic, of a scavenger receptor protein whose amino acid sequence deviates from nature. Since there are no working examples, then one must consider the guidance provided by the instant specification and the prior art of record. The instant specification provides absolutely no guidance as to which of the amino acid residues in either of SEQ ID Nos:4 and 8 of the instant application are essential for the functional and structural integrity of a scavenger receptor protein and which residues are either substitutable or expendable. Further, there is no functionally and structurally analogous

protein which has been identified in the prior art for which this information is known and could be extrapolated to a scavenger receptor protein by analogy. The instant claim encompasses isolated nucleic acids encoding a vast, almost limitless, number of scavenger receptor proteins having non-naturally occurring amino acid sequences and yet the instant specification provides no working examples and no guidance that would permit an artisan to practice the invention commensurate with the scope of the instant claims.

Appellant's argument is based upon a premise that the standard under 35 U.S.C. 112, first paragraph, is that of mutating a subject protein and testing to see if it retains the desired biological activity is a position that has been routinely dismissed by the courts, as shown by those decisions cited above. Further, *In re Wands* determined that the repetition of work which was disclosed in a patent application as producing a composition containing an antibody, which is a naturally occurring compound, did not constitute undue experimentation even if the antibody produced thereby was not identical to those that were disclosed in that application. The instant claims are not limited to naturally occurring compounds and the instant specification does not provide a description of a repeatable process of producing an isolated nucleic acid encoding a scavenger receptor protein whose amino acid deviates from either of the two disclosed, naturally occurring rodent sequences. To practice the instant invention in a manner consistent with the breadth of the claims would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner

Appellant relies upon a board decision in *Ex parte Mark*, 12 USPQZd, 1904 (Bd. Pat. App. and Int., 1989) to support an argument that 'mutate and test' is the standard under 35 U.S.C. 112, first paragraph. To the contrary, the modification of any protein by the substitution of a

different amino acid residue for a nonessential cysteine residue was enabled by that specification since the art of protein chemistry, in light of the working examples and guidance provided by that specification, was believed to be sufficiently predicable that this change could be made in any protein with a reasonable expectation that the modified protein would retain its original function and that the disclosed advantages of making this modification would be realized. The inventive contribution of *Mark et al.* was not a particular protein product but a specific modification which could be made to any protein with a reasonable amount of predictability and which would achieve a disclosed and specific advantageous result. The teachings of *Mark et al.* are specific and finite, i.e. to mutate the cysteine residues, of which there are only a few in most proteins; whereas the instant claims are, for any practical purpose, infinitely broad, and are not supported by any specific instructions as to which amino acids can be manipulated. The Board decision in *Mark* et al. therefore, does not support Appellant's position and it is not in conflict with the instant rejection.

Appellant argues that the artisan could readily identify critical amino acid residue by comparing the mouse and hamster sequences and using computer programs. This argument has been fully considered but not deemed persuasive. As reviewed by Bowie et al. (supra) it is simply impossible to predict what the effect of any amino acid substitution may have on the functional integrity of given protein. And nor is the examiner aware of any computer programs available at the time the invention was made that allow the artisan to pick non-critical amino acids, see also Ngo et al., in The Protein Folding Problem and Tertiary Structure Prediction (1993), Birkauser, Boston, pages 492-495 . One skilled in the art appreciates that the

specification has simply invited the artisan to begin an essentially random, trial and error, plan of experimentation to try to practice what is claimed.

With regard to the propriety of specifically considering the decisions of *In re Fisher*, *Amgen Inc. v. Chugai*, and *In re Wands* to the exclusion of the plurality of decisions cited by Appellant in determining the patentability of the instant claims, Appellant is encouraged to review the discussion of 35 U.S.C. 112, first paragraph in a recent CAFC decision, *Genentech. Inc. v. Novo Nordisk*, 42 USPQZd, 100 (CAFC 1997), in which these three decisions were considered as the controlling precedents in determining enablement issues where protein and recombinant DNA issues are concerned. These decisions have been relied upon in the instant rejection and by the court because they show that the judicial interpretation of the first paragraph of 35 U.S.C. 112 requires that the breadth of claims must be based upon the predictability of the claimed subject matter and not on some standard of trial and error. To argue that one can make material embodiments of the invention and then test for those that work in the manner disclosed or that the instant claims only encompass the working embodiment is judicially unsound. Unless one has a reasonable expectation that any one material embodiment of the claimed invention would be more likely than not to function in the manner disclosed or the instant specification provides sufficient guidance to permit one to identify those embodiment which are more likely to work that not without actually making and testing them then the instant application does not support the breadth of the claims. In the instant case, it is highly improbable that any artificially substituted nucleic acid which hybridizes to one of the two disclosed nucleic acids specified conditions will encode a protein which will more likely than not perform in the manner disclosed and the instant specification.

(b)The specification has not provided an enabling disclosure for species homologs of SEQ ID NO: 3 and 7, as set forth above in item 10(a)(ii)(b). Appellant argues that the Appellant has demonstrated actual reduction to practice in the application as filed for nucleic acids encoding the mouse and hamster SR-BI proteins, and are thus enabled for other species. This argument has been fully considered but not deemed persuasive. Particularly, there was no constructive reduction to practice for the human homolog. Appellant Argues that the Declaration under 37 CFR 1.131 demonstrates that this information was sufficient to screen data bases to obtain the sequence encoding the human homolog. This argument has been fully considered but not deemed persuasive, however the examiner admits that he may not understand Appellant's intention. The Declaration under 37 CFR 1.131, received 1/20/98, asserts that as of September, 5, 1993 the human homolog was not in the database, whereas sometime afterward, Appellant used the disclosed sequences to identify the human homolog after it was entered by someone else into the database. So, it appears that Appellant is suggesting that the specification enables an artisan to find the human homolog by inviting him to wait for someone else to clone it and then use the instantly disclosed sequences to find it in a database The artisan would not consider that to be adequate teaching. Further, regarding the isolation of genomic DNA, the examiner can find no evidence, in either the instant specification, nor the Declarations filed 2/14/03 (Paper 43) and 1/5/1998 (Paper 9) of constructive reduction to practice of the genomic DNA encoding human SR-BI or any other species at the time of filing, although it should be pointed out that the human gene became available with the publishing of Cao, G., et al. (supra) in 1997. The examiner can find no evidence that Appellant has proven that the specification enables others to isolate the

genomic DNA encoding human SR-BI proteins, as alleged by Appellant at page 13, middle paragraph of the Brief.

At page 14, line 5, of the Brief, Appellant asserts that "cDNA encoding SR-BI, just as appellants describe in their application, was not only used to isolate the genomic DNA encoding SR-BI , but also polymorphic variants". This argument has been fully considered but not deemed persuasive. The cDNA, to which Appellant refers, is not described in the instant Application. In example 1 of the 5,998,141 patent, to which Appellant refers, a Human SR-BI cDNA was used to screen a Human Bacterial Artificial Chromosome (BAC) library. The instant specification does not describe or enable a human SR-BI cDNA and nor does the instant specification say anything about a BAC library. Such libraries were not routinely used to clone genes at the time of filing of the instant specification.

To the contrary, the state of the art of cloning genomic mammalian DNA, at the time the invention was made, recognized that much labor and experimentation could be expected in the endeavor. In fact, the specification does not even appear to suggest any specific methodologies as to how this is to be accomplished, e.g. passing reference to the idea of genomic libraries is made at page 34, line 33, but no teachings follow. Sambrook et al, 1989 Molecular Cloning: A Laboratory Manual, is cited at page 35. Sambrook et al. is recognized as a leading authority on molecular cloning at the time the instant Application was filed. Beginning at page 9.5, Sambrook et al. review the state of the art regarding cloning of eukaryotic genes:

> "Although vectors based on bacteriophage have been extremely powerful tools for the isolation of both cDNA and genomic versions of many eukaryotic genes, they can only accommodate inserts that fall within a defined size range. Currently available bacteriophage vectors can accommodate inserts approximately 24 kb in size, and cosmid vectors can accommodate inserts of approximately 35-45 kb in

> length. In the past few years, it has become obvious that many genes are too large to be cloned as a single fragment from these vectors. For example, the gene for human factor VIII is 180 kb in length and the dystrophin gene is at least 1800 kb in length. Furthermore efforts to map and clone large segments of eukaryotic chromosomes have been hindered by the small size of the individual steps that can be achieved during chromosome walking".

In the Declaration filed 2/14/03 (Paper 43) Appellant argues that it was routine to screen genomic libraries using cDNA probes as much as a decade before the filing of the instant application. Appellant provides two examples wherein a gene was cloned from the corresponding cDNA of the same species and one example wherein a mouse gene was cloned using the human cDNA, i.e., Degrave, W. et al., Molec. Biol. Rep. 11(57-61)1986. One skilled in the art, at the time of filing of the instant application, would appreciate that the *technique* of library screening using probes designed from cDNA was routine in the art, as Appellant suggests, in that it was done routinely by many laboratories, but the skilled artisan would not view the cloning of the entire coding sequence of a human gene using a hamster cDNA as routine. That this has been done and reported in the literature, and that the skilled artisan would think it would likely be *possible* for a given hamster cDNA, does not make this endeavor routine - particularly regarding a protein as large as SEQ ID NO: 4. In *Enzo Biochem, Inc. v Calgene, Inc.* 188 F.3d 1362, 1371-72, 52 USPQ2d 1129, 1136 (Fed. Cir. 1999), it was noted that although Enzo attempted to admit post-trial evidence that included nearly one hundred technical articles which were offered at trial that described successful antisense experiments, the CAFC took the view that the district court's comprehensive opinion indicates that the court carefully considered a voluminous amount of competing evidence and testimony, and determined that the district court did not err in concluding that the generic claims directed to antisense technology in

eukaryotic cells were nonenabled. The protein of interest in the Degrave, W. et al. article was only 153 amino acids in length, the entire gene fitting on a genomic fragment of only 11.5 kb (see col 1 of page 60) - well within the recognized limits of the cloning systems available (see above). The instant polypeptide of 509 amino acids would not be expected to fit so conveniently. Cao, G., et al. (supra), report the isolation of the entire human SR-BI gene. Using a state of the art human P1-derived artificial chromosome library, Cao, G., et al. found that the gene residing on a 120 kb fragment of genomic DNA (see col 1 of 33069); the gene, itself, was found to occupy approximately 75 kb. Thus, regardless of whether or not one skilled in the art would view the work of Degrave, W. et al. as being simply routine in the art (e.g. one may be reasonably sure that the authors of Degrave, W. et al. would not view it as such) the difference between the cloning problem presented to Degrave, W. et al. is qualitatively and quantitatively different than the cloning problem confronted by Cao, G., et al., as it is also qualitatively and quantitatively different from the cloning problem presented to the highly skilled artisan who is trying to practice the invention as claimed.

In the first full paragraph of page 17 of the Brief, Appellant argues claims 11 and 19 do not make reference to particular species or non-rodent species. This argument has been fully considered but not deemed persuasive. Claim 19, which is encompassed by parent claim 11, specifically requires a human scavenger receptor. Appellant argues that all that is necessary is to have SEQ ID NO: 3 and 7 and to screen an available library. This argument has been fully considered but not deemed persuasive. To which library is Appellant referring? Appellant argues that Yang et al. (PNAS 87(7097-7911)1990) demonstrate that P1- established libraries were routine in the art. This argument has been fully considered but not deemed persuasive.

The clone of Yang was only 11 Kb, similar to that of and of Degrave, W. et al (supra) discussed above, and the skilled artisan would not have a reasonable expectation of success that using these types of vectors would produce the full length clone, as has already been discussed. Further, the Rouleau technique does not produce clones encoding functional proteins, it is simply a way to map a chromosome. Reliance on Ioannou et al. is unpersuasive for two reasons. This is a first report of an experimental library that would be expected to have inserts of the appropriate size, but the skilled artisan could not have a reasonable expectation that the library would contain a fragment corresponding to the human SR-BI gene, e.g., there were only 15000 clones in the library. These clones are randomly generated from genomic DNA, the great majority of which is believed to not encode proteins, and further, in 1994, the genome was thought to contain more than 40000 genes. Given these facts, one would not need a precise calculation of the probability of finding a clone containing the SR-BI gene in this particular library to know that the probability is remote. Thus, there would be a low expectation of success using this library to clone this particular large gene. Secondly, this single experimental report came out just 5 months before the effective priority date of the instant application, so its use by one skilled in the art could not be viewed as routine.

(c) The specification does not provide an enabling basis for allelic variants of SEQ ID NO: 3 or 7, as set forth above in item 10(a)(ii)(c). The clams encompass naturally occurring allelic variants of SEQ ID NO: 3 or 7, yet the specification failed to teach where to look for naturally occurring allelic variants of SEQ ID NO: 3 or 7, e.g. no specific disorder or specific phenotype has been asserted to correlate with a naturally occurring allelic variant, such that the artisan might know where to obtain a variant. The specification merely offers the skilled artisan

the invitation to randomly try to find variants through trial and error sampling of animal populations. Such random trial and error experimentation is unduly burdensome.

At page 14 of the Brief, Appellant argues that proof of enabling basis for allelic variants is found in U.S. Patent No: 5,998,141. This argument has been fully considered but not deemed persuasive. It does not appear that any of the multitude of human polynucleotide sequences or primers that are disclosed in examples 1-4 of the '141 patent are disclosed in the instant application.

(d) The specification does not provide an enabling basis for the administration of a compound that selectively inhibits binding of lipoprotein to the scavenger receptor protein type BI, as required by claim 49, as set forth above in item 10(a)(ii)(d). The specification provides no such compound, but merely an invitation to find such a compound, if such a compound can be found. One highly skilled in the art appreciates that the screening assays described on pages 43-54 are useful for determining whether or not a compound selectively inhibits binding of lipoprotein to the scavenger receptor protein type BI; and although they are useful in the search for such compounds, they do not automatically produce the compounds. The invitation to use these assays to search for compounds having the desired properties is simply an invitation for further research and investigation to randomly sample any and all compounds for the desired activity. Such random experimentation is unduly burdensome.

On page 18 of the Brief, Appellant urges that working examples are provided. This argument has been fully considered but not deemed persuasive. Presumably Appellant is referring to the experiments depicted in Figures 3, 5, 7, and 8 wherein BSA and certain lipids are shown to inhibit the binding of AcLDL to the hamster SR-BI protein expressed in COS cells -

which are monkey kidney cells. First it should be pointed out that the claim is limited to inhibiting the binding of lipids to adipocytes, thus Appellant's assertion that there are working examples is not correct. Importantly, however, the claims encompass the use of inhibitors that are contemplated in the specification without an enabling teaching as to how to obtain such inhibitors, e.g. through random screens and computer modeling, etc. (e.g. pages 43-47). The skilled artisan appreciates that these teachings are simply suggestions to the skilled artisan to begin a research plan of essentially random trial and error experimentation to try and find compounds that can be used commensurate with that being claimed. The inhibition experiments disclosed in the specification have simply used the several endogenous ligands of the receptor as inhibitors of each other; this does not provide adequate teaching as to how to make compounds that would inhibit these interactions as contemplated in the specification.

Additionally, at page 33(e) of the Brief, Appellant appears to be addressing some aspect of the rejection that the examiner is unaware of. As set forth above, the instant specification is not enabling for methods of inhibiting uptake of lipoproteins or lipids by adipocytes comprising administering a genus of compounds that selectively inhibit the binding of lipoprotein to an SR-BI protein, as required by claim 49.

(e) Appellants additional arguments, set forth in items (a)-(f) on pages 32-34, regarding enablement for claims 44-50 have been fully considered but not deemed persuasive. The claims are directed to methods that require the use of a genus of SR-BI proteins that which the specification has failed to provide adequate teaching as to how to make without undue experimentation, as fully discussed in items 10(a)(ii)(a-c) above.

Appellant's arguments on page 34 regarding claim 50 are unpersuasive. The issue is that the specification has not taught how to use polypeptide sequences other than those encoded by SEQ ID NO: 3 and 7 to raise antibodies that are specific to any SR-BI protein other than those encoded by SEQ ID NO: 3 and 7. Nor has the specification taught how to identify any SR-BI protein other than those encoded by SEQ ID NO: 3 and 7. Neither has the specification taught what sequences are useful for identifying polynucleotides of SEQ ID NO: 3 or 7 other than those polynucleotide themselves.

11(b) Claims 11-13, 19-22, 44-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Appellant regards as the invention, as set forth above and reiterated below:

(a) Claims 11 and 50 and dependent claims 12, 13, 19-22 require, a "functional" scavenger receptor protein type BI (claim 11), or method comprising determining "the function" of scavenger receptor protein type BI (claim 50). As used in the art to describe a newly isolated protein that has been characterized in various in vitro assays, the word "function" is of dubious value in establishing and describing the sphere of biologic properties that a protein may have in an intact organism. The word "function" implies more than a list of physical properties, and is more akin to the idea of a biologic role for the protein. The instant specification has not set forth what aspects of the scavenger receptor protein type BI define its function or biologic role. The specification, at pages 29-30, merely hint at, and in a generalized way, potential biologic roles for the protein, e.g. that the data provide support "for the potential role of this receptor in lipoprotein and lipid metabolism", see page 29, Lines 19-20. In fact, the specification as filed

(other than claim 50) does not appear to use the word "function" in relation to the scavenger receptor protein type BI. Thus, the artisan could not reasonably and unambiguously know whether or not he or she was practicing the claimed invention, because he or she would not know what is meant by the term "function" or "functional" in relation to the claims.

Appellant argues that "clearly the examiner fully understands what is meant by the claims. This argument has been fully considered but not deemed persuasive for the reasons set forth above.

Appellant argues that hundreds of patents have issued using the language now pending and, particularly, the issued Acton patent. This argument has been fully considered but not deemed persuasive. Regarding the assertion that hundreds of patents have issued using the language now pending, the examiner maintains that it is the instant claims, having the instant fact-pattern, that are now under examination. Regarding the issued Acton patents, the examiner can find no use of the word "functional" in any issued claims, nor any language directly relevant to the remaining issues below.

(b) Claims 11-13, 19-22, 44-50 require a vast, and essentially limitless, number of proteins that are "scavenger receptor protein type BI" proteins, yet the claims do not set forth that element or combination of elements that is unique to or definitive of a "scavenger receptor protein type BI", as set forth above and elaborated upon below.

(b)(i)Regarding the defining properties, on the claims, of the stringency conditions recited in the claims, Appellant argues that moderately stringent conditions are defined at page 10, lines 24-31, and that, essentially, the claims are definite because one would know how to determine the melting temperature of a perfectly matched double stranded DNA molecule. This

argument has been fully considered but not deemed persuasive. There appears to be a simple misunderstanding between Appellant and the examiner with regard to how the teachings at page 10 relate to the way the claims are currently worded. As currently worded, the melting temperature of the perfectly base-paired double stranded DNA provides the reference temperature with which the nucleic acid encoding the "scavenger receptor protein type BI" must hybridize, i.e. at 25°C below the melting temperature of the perfectly base-paired double stranded DNA. Thus, the melting temperature of the perfectly base-paired double stranded DNA determines the bounds of the claims. If, for example, the perfectly base-paired double stranded DNA were very long and have a high GC content, then it would have a higher melting temperature than a perfectly base-paired double stranded DNA that was shorter or had less GC content. The higher the melting temperature of the reference perfectly base-paired double stranded DNA, the higher the hybridization temperature and thus the number of potential molecules that could hybridize to SEQ ID NO: 3 or 7 would diminish as the melting temperature increased. These facts are clearly articulated by the specification at pg 40, Lines 18-35. The problem with the claims is that they do not set forth *which* perfectly base-paired double stranded DNA *is* the reference polynucleotide. And nor do the claims or specification indicate that *any* perfectly base-paired double stranded DNA could serve as the reference DNA, as one skilled in the art would not expect that to be possible and would not consider that to be a reasonable interpretation of the claims. Thus, this is not a matter of a undue breadth, as argued by Appellant. Therefore, in the vast continuum of hybridization conditions required by the claims, it is unclear what conditions are meant to provide meaning and definitiveness to the phrase "scavenger receptor protein type BI". One of ordinary skill in the art would view the teachings

of the specification at pg 40, Lines 18-35, as they relate to hybridization to SEQ ID NO: 3 or 7, to mean that the reference polynucleotide ***is*** a perfectly base-paired double stranded DNA consisting of SEQ ID NO: 3 or 7. Yet, this is not what is currently being claimed. See suggested claim language above. It is unclear if Appellant has directly addressed this aspect of the reject.

(b)(ii) Furthermore, claim 11 requires "moderately stringent conditions" whereas claim 13 requires "stringent" conditions, yet each recite that the conditions are that produced at a temperature of approximately 25°C below the melting temperature of the perfectly base-paired double stranded DNA. Thus, it is unclear what difference is meant, if any, between the "moderately stringent conditions" of claim 11 and the merely "stringent" conditions of claim 13. It is unclear if Appellant has directly addressed this aspect of the rejection.

(b)(iii) Additionally, claims 11, 44, 48 and 49 recite the limitation "which selectively binds to low density lipoprotein and to modified lipoprotein". This phrase is not sufficient, either alone, or in conjunction with the other limitations recited in the claims, to provide a meaningful definition of the phrase "scavenger receptor protein type BI". Further, the specification does not teach that these limitations are definitive of a "scavenger receptor protein type BI". At page 10, line 39 bridging page 11, the specification teaches that hsSR-BI differs from CD36 and other modified lipoprotein receptors described to date in that its binding of AcLDL is inhibited by native LDL.

Appellant argues that the two disclosed SR-BI sequences are adequate to define a cDNA encoding SR-BI. This argument has been fully considered but not deemed persuasive. The claims are not limited to these two sequences, and the specification clearly indicates that other sequences are encompassed by the invention, e.g. pg 6.

Appellant's additional arguments on pages 44-46 regarding claims 44-50 have been fully considered but not deemed persuasive for the reasons discussed above.

11(c) Claims 11, 13, 19, 20 and 22 are rejected under 35 U.S.C. 102(a) as being anticipated by Calvo et al., J. Biol. Chem. 268(25)18929-18935, Sept. 05, 1993.

Figures 2 and 3 on pages 18931 and 18932 of Calvo provide the nucleotide sequences of a recombinant nucleic that Appellant has admitted is the human equivalent of the mouse and hamster SR-BI, e.g. the Declaration filed 1/5/98 (Paper 9), that would be expected to hybridize under the conditions of the claims, absent evidence to the contrary. Further the labeled nucleic acid of claim 20 can be found in Figure 5 on page 18993. Additionally, host cells comprising the isolated nucleic acid (claim 22) were used in the cloning and sequencing of the nucleic acid, e.g. col 1 of page 18932.

Appellant argues that Calvo do not teach each and every feature of the claimed nucleic acid, e.g. that Calvo do not teach the function of the encoded protein. This argument has been fully considered but not deemed persuasive. What protein is encoded by the nucleic acid is an inherent and necessary part of that nucleic acid. The examiner can find no reason why the protein encoded by the nucleic acid disclosed by Calvo would not be the same as that claimed. Calvo identifies the nucleic acid in Fig. 2. The functional activity of the encoded protein is an inherent property of the nucleic acid. The claims do not require an expression vector. Appellant further argues that Calvo does not identify conditions under which the other SR-BI encoding molecules could be isolated. This argument has been fully considered but not deemed persuasive because Calvo need only anticipate one embodiment of the claim.

Appellant's arguments regarding the 1.131 Declaration and case law are unpersuasive. The Declaration clearly indicates that prior to the publication of Calvo Appellant was in possession of only the DNA encoding the hamster SR-BI. As discussed in great detail under the written description rejection, this single cDNA is not sufficient to describe the claimed genus, *In re Spiller* and *In re Zletz*; nor is it sufficient to render obvious the human DNA described by Calvo, *In re Clarke*. Thus, Appellant does not show priority to the species disclosed by the reference, *In re Stemple* and *In re Schaub*.

Appellant's arguments beginning in the first paragraph of page 53 are confusing. Appellant appears to argue that because Appellant was aware of rat LimpII and CD36 , then Appellant was in possession of the genus of SR-B1 proteins. The examiner was under the impression that these proteins were not considered by Appellant to be members of the genus of SR-B1 proteins (e.g. page 52). That Appellant was not in possession of the genus of SR-BI proteins encompassed by claims 11, 13, 19, 20 and 22 at the time of filing has been thoroughly discussed above.

11(d) Claims 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Calvo et al., J. Biol. Chem. 268(25)18929-18935.

Claim 21 requires an expression vector comprising the polynucleotide of claim 11. Although Calvo et al expressed the protein as a fusion with CD36 because antibodies to their new protein were not available (pg 18933, col 1), it would have been obvious to one of ordinary skill in the art, i.e. a biomedical research scientist, to express the CLA-1 protein by incorporating the cDNA described therein into an expression vector and heterologous host by employing those

methods which are routine in the art at the time the invention was made to permit the quantitative production of CLA-1 and to facilitate its characterization at the molecular level, particularly to conduct assays for binding partners of the polypeptide as suggested in col 2 page 1893 of Calvo, as would be commonly understood in the art.

Appellant's arguments regarding the Declaration as antedating Calvo have been discussed above and are not persuasive. Appellant's additional arguments on pages 58 and 59 do not appear to be germane to the instant claim 21.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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March 25, 2004

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